REMARKS

Claims 1-6 and 11-19 are pending in the subject application. No claim has been added, canceled, or amended herein. Accordingly, claims 1-6 and 11-19 are still pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's objection and rejections made in the November 4, 2003 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides methods for treating or preventing an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts. In the preferred embodiment, the inflammatory disease is psoriatic arthritis.

Formalities

The Examiner objects to applicants' claim that the instant claims maintain priority back to U.S. Serial No. 07/958,248, filed October 8, 1992. The Examiner alleges that the filing date of the instant claims is the filing date of parent application U.S. Serial No. 08/690,775, filed August 1, 1996. Specifically, the Examiner asserts that priority application U.S. Serial No. 08/403,785 and PCT/GB94/00462 do not support the broader claims of the

instant application, including "preventing a tumor necrosis factor-mediated disease", "tumor factor-mediated disease", "binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 58-80", "cA2" and "epitope of cA2".

In response, applicants note that the instant claims do not recite the phrase "preventing a tumor necrosis factor-mediated disease", or "tumor factor-mediated disease". Thus, the Examiner's objection based on these phrases is obviated.

With respect to the remaining phrases, applicants maintain that the pending claims are entitled to a priority date of October 8, 1992, the filing date of U.S. Serial No. 07/958,248 (the "'248 Application").

Under 35 U.S.C. §120, a claim in a U.S. application is entitled to the benefit of the filing date of an earlier filed U.S. application if the subject matter of the claims is disclosed in the manner provided by 35 U.S.C. §112, first paragraph, in the earlier filed application. M.P.E.P. §201.11(I). It is well settled that "[t]he subject matter of a claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." M.P.E.P. §2163.03. Furthermore, a claim is supported by the disclosure in an application "when that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." M.P.E.P. §2164.01.

Applicants maintain the '248 Application discloses the subject matter of claims 1-6 and 11-19 in the manner provided by 35 U.S.C. §112, first paragraph. The '248 Application, at page 4, lines 27-32, teaches the treatment of autoimmune disease and inflammatory disease with anti-CD4 antibodies in combination with anti-TNF antibodies (see also, e.g., page 6, lines 5-8). At page 11, line 17 to page 12, line 4, the '248 Application teaches that combination therapy claimed in the instant invention can be used to treat autoimmune and inflammatory diseases, including psoriatic arthritis (page 11, line 25).

At page 10, lines 6-9, the '248 Application specifically teaches the use of methotrexate in conjunction with an anti-TNF antibody. At page 6, line 8 to page 7, line 26, and page 8, lines 13-33, the '248 Application teaches anti-TNF antibodies, including chimeric antibodies (page 6, lines 13-17 and 21-29). At page 11, lines 1-6, the '248 Application describes the use of other agents (TNF antagonists) which interfere with TNF, TNF receptor signaling or TNF synthesis.

Thus, the '248 Application provides support in the manner provided by 35 U.S.C. §112 for claims 1-6 and 11-19. Similarly, parent applications, including U.S. Serial No. 08/403,785 and PCT/GB94/00462, provide support for these claims. Accordingly, the instant claims are entitled to a priority date of October 8, 1992, the filing date of the '248 Application.

Rejection Under 35 U.S.C. §102(e)

The Examiner rejected claims 1-6, 11, 13, 14 and 19 under 35 U.S.C. §102(e) as allegedly anticipated by Mak et al. (U.S. Patent No. 6,190,691; "Mak").

In response to the Examiner's rejection, applicants respectfully traverse. Applicants incorporate herein by reference their remarks in the June 17, 2003 Amendment made in connection with the alleged anticipation of the claimed subject matter, and make the following additional remarks to underscore their position.

Briefly, claims 1-6, 11, 13, 14 and 19 provide methods for treating or preventing an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts. In preferred embodiments, the inflammatory disease is psoriatic arthritis and the TNFα antagonist is an anti-TNFα antibody or antigen-binding fragment thereof.

Under 35 U.S.C. §102(e), and as stated in M.P.E.P. §2131.01, "[a] claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (emphasis added). Hence, to anticipate the methods of claims 1-6, 11, 13, 14 and 19, Mak would have to teach each and every element thereof.

Mak fails to do this.

Mak states that the pharmacological agents which are useful in this aspect of the invention are from a *broad* range of agents known in the literature for other diverse activities (column 30, lines 2-4). Indeed, from column 29, line 60 through column 43, line 2, Mak organizes the agents into several groups, each group containing representative examples, the combined total of these examples numbering in the *hundreds*.

Although methotrexate and TNF antagonists are disclosed in Mak, there is no specific disclosure of the *claimed combination* of methotrexate and a TNFα antagonist, or of methotrexate and anti-TNFα antibody, to treat or prevent an inflammatory disease. In fact, Mak only *generally* discloses combination therapies as evidenced by the following: "combination of occlusion and pharmacological agents" (column 53, lines 8-9; column 57, lines 65-67), "combination of pharmacological agents" (column 63, lines 15-18; column 58, lines 5-6), "anti-inflammatory agent...in combination with one or more different drugs" (column 55, lines 24-30) and "pharmacological agents...in combination with a penetration blocking agent" (column 60, lines 40-44).

Contrary to the Examiner's assertion that Mak discloses the claimed species, Mak actually discloses a broad genus encompassing an astronomical number of possible combination therapies, only one of which combinations is recited in the instant claims. Applicants stress that teaching a broad genus from which a specific species is claimed does not constitute disclosing the claimed

species. Without specifically teaching the claimed species, one skilled in the art would not be able to envisage the claimed species from an extremely broad statement such as "combination of pharmacological agents" or "anti-inflammatory agent...in combination with one or more different drugs" with the broad range of agents disclosed in Mak. Thus, Mak fails to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 1-6, 11, 13, 14 and 19 satisfy the requirements of 35 U.S.C. §102(e).

Rejection Under 35 U.S.C. §103 - Obviousness

The Examiner also rejected claims 1-6, 11-14 and 16-19 under 35 U.S.C. §103 as allegedly unpatentable over Mak and/or Adair et al. (U.S. Patent 5,994,510; "Adair") in view of Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437; "Merck") and Aggarwal et al. (U.S. Patent No. 5,672,347; "Aggarwal").

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants incorporate herein by reference their remarks in the June 17, 2003 Amendment made in connection with the non-obviousness of the claimed subject matter, and make the following additional remarks to underscore their position.

Again, claims 1-6, 11-14 and 16-19 provide methods for treating or preventing an inflammatory disease in an

individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts. In preferred embodiments, the inflammatory disease is psoriatic arthritis and the TNFα antagonist is an anti-TNFα antibody or antigen-binding fragment thereof.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, Mak and/or Adair, when combined with Merck and Aggarwal, fail to provide a motive to combine and a reasonable expectation of success.

As discussed above, Mak does not teach or suggest a combination of methotrexate and a TNFα antagonist, or of methotrexate and anti-TNFα antibody, to treat or prevent an inflammatory disease.

Adair teaches the use of recombinant anti-TNF antibody to treat immunoregulatory and inflammatory disorders. Nowhere does Adair mention or suggest methotrexate or its combined use with a TNF antagonist or anti-TNF antibody.

Merck teaches the sole use of methotrexate in the treatment of inflammatory disease. Merck does not mention or suggest combining a TNF antagonist or an anti-TNFα antibody with methotrexate to treat psoriatic arthritis.

Like Mak, Adair and Merck, Aggarwal also fails to provide motivation to combine these references, or a reasonable expectation of success. Aggarwal teaches that TNF antagonist can be used in combination with anti-inflammatory agents such as gold colloids, cyclosporin antibiotics, salicylate and corticosteroids such as methylprednisolone, and that the employment of these listed agents with TNF antagonists can be used in lesser dosage than when used alone. (Aggarwal, column 7, lines 60-64.) Applicants note, however, that methotrexate or the combination of methotrexate and a TNF antagonist is not disclosed in the above example or anywhere else in Aggarwal. Essentially, nowhere in Aggarwal is there any mention or suggestion to use methotrexate in combination with an anti-TNFα antibody (or TNFα antagonist generally) in the treatment of inflammatory diseases.

According to the M.P.E.P. §2143.01,

> "[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

In re Mills, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which parameters [are] critical or [a] direction as to which of many possible choices is likely to be successful" to one skilled in the art to use methotrexate with a TNFα antagonist or anti-TNFα antibody to treat psoriatic arthritis. (*In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).) Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection. (*O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988))

Finally, applicants note that the claimed invention demonstrates an unexpected advantage, e.g., inducing high clinical response rates for significantly longer duration in comparison with those obtained with treatment with each therapeutic modality separately. This unexpected synergistic effect is evidenced in Figures 1A, 2A, 3A, 4A, and 5A and Table 4 of the instant application. (See also, e.g., page 3, lines 18-24, Examples 1-3; particularly, page 35, lines 5-8, page 37, lines 1-3, pages 36-37

(Table 3), pages 38-39 (Table 4), page 46, line 24 through page 47, line 8 of Example 1; page 48, line 20 through page 50, line 8 of Example 2; and page 51, lines 8-32 of Example 3). The magnitude of these results, particularly in the treatment of inflammatory disease, could not have been predicted from the cited references. Thus, to the extent a proper *prima facie* case were made by the Examiner, which, again, applicants do not concede, this evidence of a surprising, i.e., synergistic, result over treatment with either methotrexate or TNFα antagonist alone would overcome such case. (See M.P.E.P. §716.02.)

Applicants reiterate that, clearly, these experimental results are unexpected, especially when viewed in light of the teaching of Verhoeven et al. (cited and discussed in applicants' previous response) showing that superior effects of a particular combination therapy in the treatment of inflammatory disease are *not* predictable absent experimentation.

Therefore, in view of the surprising nature of this invention, one of ordinary skill in the art would *not* have been able to predict, based on the cited references, whether administering both a methotrexate and a TNFα antagonist to an individual would treat inflammatory disease *more effectively* than either agent alone. Moreover, one of ordinary skill certainly would not have reasonably expected the superior effects over either agent alone as discussed above. To maintain otherwise would be hindsight.

In view of the above remarks, applicants maintain that claims 1-6, 11-14 and 16-19 satisfy the requirements of 35 U.S.C. §103.

The Examiner also rejected claims 14-15 under 35 U.S.C. §103 as allegedly unpatentable over Mak and/or Adair in view of Merck and Aggarwal as applied to claims 1-6, 11-14 and 16-19 above and further in view of Le et al. (U.S. Patent No. 5,919,452; "Le").

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Claims 14 and 15 provide methods for treating or preventing an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and the chimeric anti-TNFα antibody cA2, or a competitive inhibitor thereof, to said individual, in therapeutically effective amounts.

Mak, Adair, Merck and Aggarwal are discussed above.

Le fails to cure the deficiencies of the other cited references. Like Adair and Aggarwal, Le does not mention or suggest the use of methotrexate or its combined use with a chimeric anti-TNFα antibody in the treatment of inflammatory diseases. Le merely teaches the use of chimeric anti-TNFα antibodies, including cA2, to treat TNF-related pathologies. Thus, even with Le, the combination of cited references does not create a motivation to combine.

As mentioned above, the claimed invention is based on an unexpected advantage of combining methotrexate and anti-TNFα antibody, e.g., inducing high clinical response rates for significantly longer duration in comparison with those obtained with treatment with each therapeutic modality separately. The magnitude of these results, particularly in the treatment of inflammatory disease, could not have been predicted from the cited references. Thus, to the extent a proper *prima facie* case were made by the Examiner, which, again, applicants do not concede, this evidence of a surprising, i.e., synergistic, result over treatment with either methotrexate or a chimeric anti-TNFα antibody alone would overcome such case.

Again, the collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of applicants' invention and underlying discovery. Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result. Again, devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection. (*O'Farrell* at 903)

In view of the above remarks, applicants maintain that claims 14-15 satisfy the requirements of 35 U.S.C. §103.

Rejection Under Obviousness-Type Double Patenting

The Examiner rejected claims 1-6 and 11-19 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-30 of U.S. Patent No. 6,270,766 (the "'766 Patent").

Applicants inadvertently omitted a response to this rejection in their June 17, 2003 Amendment.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants intend to file a terminal disclaimer with respect to the '766 Patent once the claims are otherwise in condition for allowance.

Provisional Rejection Based On Statutory Double Patenting

The Examiner provisionally rejected claim 1-6 and 11-19 under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 32-37, 42-50, 55-64 (or appropriate pending claims) of copending U.S. application Serial No. 09/921,937.

Applicants inadvertently omitted a response to this rejection in their June 17, 2003 Amendment.

In response, applicants request that the Examiner hold this provisional rejection in abeyance until one of the two applications is allowed. Furthermore, applicants point out that subject to this application being otherwise allowable and copending application Serial No.

09/921,937 being allowed, applicants intend to cancel any claims in this application which are in fact directed to the same subject matter claimed in a different application.

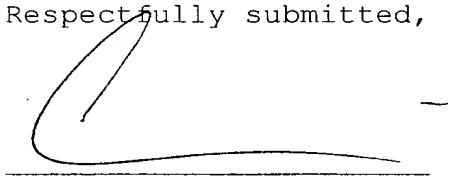
Summary

Applicants maintain that the claims pending are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

2/4/04

Alan J. Morrison
Reg. No. 37,399

Date